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RESEARCH ARTICLE

# Rare Coagulation Factor Deficiencies: Multicenter Experience With 188 Cases

**Veysel Gök[1,2], Esra Pekpak Şahinoğlu[3], Hüseyin Tokgöz[4], Fatma Türkan Mutlu[2], Can Acıpayam[5], Kamuran Karaman[6], Defne Ay Tuncel[7], Ayşe Ceyda Ören[3], Ayşe Şimşek[4], Bilal Arslan[6], Hatice Beyza Ünal[1], Alper Özcan[1], Ebru Yılmaz[1], Sinan Akbayram[3], Musa Karakükçü[1], Ahmet Fayik Öner[6], Ümran Çalışkan[4], Türkan Patıroğlu[1], Ekrem Ünal[1,8]**

[1]Erciyes University Faculty of Medicine, Division of Pediatric Hematology and Oncology, Department of Pediatrics, Kayseri, Türkiye
[2]Health Sciences University, Kayseri City Hospital, Department of Pediatric Hematology and Oncology, Kayseri, Türkiye
[3]Gaziantep University Faculty of Medicine, Division of Pediatric Hematology and Oncology, Department of Pediatrics, Gaziantep, Türkiye
[4]Necmettin Erbakan University Meram Faculty of Medicine, Division of Pediatric Hematology and Oncology, Department of Pediatrics, Konya, Türkiye
[5]Sütçü İmam University Faculty of Medicine, Division of Pediatric Hematology and Oncology, Department of Pediatrics, Kahramanmaraş, Türkiye
[6]Van Yüzüncü Yıl University Faculty of Medicine, Division of Pediatric Hematology and Oncology, Department of Pediatrics, Van, Türkiye
[7]Health Sciences University, Adana City Hospital, Department of Pediatric Hematology and Oncology, Adana, Türkiye
[8]Hasan Kalyoncu University, Department of Nursing, Faculty of Health Sciences, Gaziantep, Türkiye

**ORCID ID:** V.G. 0000-0002-7195-2688; E.P.Ş. 0000-0003-2143-1435; H.T. 0000-0002-3064-4646; F.T.M. 0000-0003-4593-8679; C.A. 0000-0002-6379-224X; K.K. 0000-0003-2991-3551; D.A.T. 0000-0002-1262-8271; A.C.Ö. 0000-0002-7676-0095; A.Ş. 0000-0001-9250-078X; B.A. 0009-0001-3907-0888; H.B.Ü. 0000-0002-5684-5657; A.Ö. 0000-0002-6100-1205; E.Y. 0000-0003-4802-0986; S.A. 0000-0001-7410-4310; M.K. 0000-0003-2015-3541; A.F.Ö. 0000-0003-3858-8105; Ü.Ç. 0000-0003-4695-7046; T.P. 0000-0003-2471-764X; E.Ü. 0000-0002-2691-4826

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## ABSTRACT

**Objective:** Rare factor deficiencies are a group of autosomal recessive bleeding disorders (with the exception of dysfibrinogenemia), which are characterized by the deficiency or dysfunction of one or more coagulation factors (F)I, FII, FV, FV+FVIII, FVII, FX, FXI, FXII, and FXIII.
**Materials and Methods:** 188 patients with a rare factor deficiency from seven distinct pediatric hematology centers in Turkey were obtained for the study.
**Results:** 60 (31.9%) patients had a family history of bleeding. Consanguinity was detected in 85 patients (45.2%). 128 patients (68.1%) were symptomatic; the most common bleeding symptom was epistaxis (34.6%) and followed by the bleeding of skin (19.1%), oral cavity (16.1%), soft tissue (8%), central nervous system (CNS) (6.2%), uterine (4.9%), joint (3.7%), gastrointestinal system (GIS) (3.7%), and urinary system (US) (3.7%). The first bleeding sites consist of nose (39%), CNS (10.9%), oral cavity (10.9%), skin (10.9%), umbilical cord (10.2%), GIS (5.5%), US (5.5%), heel (4.7%), and musculoskeletal system (2.3%). CNS hemorrhage was the most common in fibrinogen (n:4), FVII (n:6), and FX (n:2) deficiency, umbilical cord bleeding was the most common in fibrinogen (n:3) and FXIII (n:7) deficiency, heel bleeding was frequently seen in fibrinogen (n:6) deficiency. The life-threatening bleedings were CNS (n:27, 77.1%), GIS (n:7, 20%), and iliopsoas (n:1, 2.9%), respectively. The reasons leading to the diagnosis were bleeding (57.4%), preoperative screening (15.4%), incidental (15.4%), family history (6.4%), and postoperative bleeding (5.3%). 2/5 FXII deficiency patients had mild bleeding symptoms.
**Conclusion:** As bleeding disorders are somehow a rare group of disorder, early diagnosis and treatment are critical to reduce the high morbidity and mortality.

**Keywords:** Bleeding, Deficiency, Factor, Rare

## INTRODUCTION

Rare factor deficiencies (RFDs) arise when one or more of the coagulation factors (FI, FII, FV, FV+FVIII, FVII, FX, FXI, FXII, and FXIII) are missing or not working properly. RFDs account for 3 to 5% of all hereditary bleeding disorders (1, 2). These factors are utilized in various stages of the coagulation cascade, leading to the formation of a stable fibrin clot (2). The exact prevalence of these disorders is uncertain due to the lack of epidemiological data and the large number of asymptomatic patients; nevertheless, the estimates range from 1:300,000 to 1:2,000,000. FVII deficiency is the most common, while FII deficiency is the rarest of all. They are seen with a low frequency and are inherited in an autosomal recessive trend besides dysfibrinogenemia (3).

**Corresponding Author:** Ekrem Unal **E-mail:** drekremunal@yahoo.com.tr

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The clinical features of RFDs have not been fully clarified. RFD may be clinically asymptomatic or associated with heavy bleeding symptoms due to some of the coagulation factors being missing or not working properly. Typical presentations are usually expected in homozygous or combined heterozygous cases; however, only mild symptoms might be observed in carrier individuals, such as FVII and fibrinogen deficiency (4). Generally, there is no correlation between the factor level and the clinical symptoms. Peyvandi et al. showed that there is a weak correlation between FV, FVII, and FXI levels and the clinical manifestations in a multinational study, while they stated that there is a strong correlation between the factor level and the clinical symptoms in fibrinogen, FX, FXIII, and combined FV+FVIII deficiencies (5). Heavy bleeding and musculoskeletal bleeding are mostly seen in fibrinogen, FII, FX, and FXIII deficiencies (6, 7). In FX deficiency, gastrointestinal system (GIS) and central nervous system (CNS) bleedings are common, while umbilical cord bleeding is more common in fibrinogen and FXIII deficiency (8, 9). Mucocutaneous bleeding is a prominent finding in individuals with FV and FXI deficiencies. On the other hand, in patients with FXII deficiency, thrombosis is more common with prolonged activated partial thromboplastin time (aPTT), accompanied by rarely mild mucocutaneous bleeding (10). In addition to bleeding, dysfibrinogenemia may be accompanied by both arterial and venous thrombosis (11).

Mucocutaneous is the most common bleeding site in RFDs, but CNS, GIS, and musculoskeletal bleeding are also common. RFD patients can be diagnosed with recurrent bleeding, postoperative bleeding, preoperative screening, and incidentally (12).

Initial laboratory tests should include prothrombin time (PT)/ aPTT, fibrinogen, thrombin time (TT), bleeding time, and a complete blood count. Only aPTT is prolonged in FXI and FXII deficiency, only PT is prolonged in FVII deficiency, and both PT and aPTT are prolonged in common pathway factor deficiencies (FII, FV, FX, FV+FVIII). Thrombin time is prolonged only in fibrinogen deficiency. However, in FXIII deficiency, all the coagulation tests (PT, aPTT, TT) are normal (2). When FXIII deficiency is suspected, a clot lysis test may be studied as a potential screening test, moreover FXIII activity and/or antigen level should be studied for a definitive diagnosis (13).

The FV+FVIII combination is the most common type of combined factor deficiency, with autosomal recessive inheritance. This is a completely different disease than the deficiency of either FV or FVIII. The deficiency of FV (autosomal recessive) and FVIII (X-linked) results from defects in their respective genes individually. However, the combined deficiency of FV and FVIII, is caused by defects in two other genes (*LMAN1* and *MCFD2*) which is regulating ERGIC and is the compartment between the endoplasmic reticulum and Golgi apparatus. This compartment controls the trafficking and exit of certain proteins, including FV and FVIII. Although FV and FVIII are synthesized in hepatocytes in full, as a result of ERGIC-53 dysfunction, the passage of these factors through the cell and their delivery to the circulation is defective (14).

In RFDs, the preferred treatment option is to replace the missing factor. Dosing is dependent on the lowest blood level and half-life of the factor. Fresh frozen plasma (FFP) can be used for most factor deficiencies during acute hemorrhage if the diagnosis is not clear, or the factor is not available. In addition, cryoprecipitate (containing more FVIII, vWF, fibrinogen, and FXIII) may be preferred in patients with a precise diagnosis, since it contains some factors in higher concentration and in lower volume. There are specific factor concentrates containing either fibrinogen, FVII or FXIII. Lastly, antifibrinolytics such as epsilon aminocaproic acid and tranexamic acid may be preferred for mild mucocutaneous hemorrhages (15).

In the current study, demographic characteristics, and bleeding profiles of 188 RFD patients from seven distinct pediatric hematology centers in Turkey were presented.

## MATERIAL AND METHOD

RFD patients from seven distinct pediatric hematology centers in Turkey were obtained. Hematology centers and number of patients; Erciyes University (n: 47), Gaziantep University (n: 37), Meram Faculty of Medicine (n: 28), Kayseri City Hospital (n: 26), Sütçü İmam University (n: 24), Yüzüncü Yıl University (n: 16), Adana City Hospital (n: 10). Demographic information, diagnoses, consanguinity, family history of bleeding, age at first bleeding and diagnosis, first and most frequent bleeding sites, life-threatening bleeding, and general bleeding profiles of the patients were evaluated. The severity of factor deficiencies was categorized as <5% severe, 5 to 30% moderate, and 30 to 50% mild. Descriptive statistics were performed, and SPSS Statistical Version 26 was used for the analysis. Informed consent was obtained from the patients and their relatives. This study was approved by the Ethics Committee of Erciyes University (Approval number: 2023/350).

## RESULTS

Of the 188 patients, 73 (38.8%) were female and 115 (61.2%) were male. The mean current age of the patients was 11.4 (4 months-33 years) years. Among these patients, 110 FVII (58.5%), 19 fibrinogen (10.1%), 14 FXI (7.4%), 12 FX (6.4%), 10 FXIII (5.3%), 8 FV (4.3%), 7 FV+FVIII (3.7%), 5 FXII (2.7%), 2 FII (1.1%), and one patient had combined deficiency of FVII and FIX. There was a family history of bleeding disorders in 60 (31.9%) patients. Consanguinity has been detected in 85 (45.2%) of the patients **(Table 1)**. Except for factor XIII deficiency, all patients had abnormal initial coagulation tests (PT and aPTT). According to factor activities, 62 patients (33%) were classified as severe, 81 patients (43.1%) were classified as moderate, and 45 patients (23.9%) were classified as mild.

FVII deficiency was detected in 38/45 (84.4%) of the patients whose factor levels were between 30-50% **(Table 1)**. 128 patients (68.1%) had bleeding symptoms at least once in their lives, and the most common symptoms were epistaxis (34.6%), skin (19.1%), oral cavity (16.1%), soft tissue (8%), CNS (6.2%), uterine (4.9%), joint (3.7%), GIS (3.7%), and urinary system (US) (3.7%) bleeding, respectively (Figure 1). 61% of symptomatic patients remained symptomatic in the last year. The first bleeding sites include nose (39%), CNS (10.9%), oral cavity (10.9%), skin

(10.9%), umbilical cord (10.2%), GIS (5,5%), US (5.5%), heel (4.7%), and musculoskeletal system (2.3%) (Figure 2,3).

CNS hemorrhage was the most common in fibrinogen (n:4), FVII (n:6), and FX (n:2) deficiency, umbilical cord bleeding was the most common in fibrinogen (n:3) and FXIII (n:7) bleeding of the heel was the most frequently seen in fibrinogen (n:6) deficiency (Table 2). The patients were classified according to the first bleeding age (Figure 4); in symptomatic 128 patients, 21.1%

**Table 1: Demographic information of the patients**

| | Fibrinogen deficiency | FII deficiency | FV deficiency | FV+FVIII deficiency FVII deficiency | FVII deficiency | FX deficiency | FXI deficiency | FXII deficiency | FXIII deficiency | FVII+FIX deficiency | Overall n (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Patients (n)** | 19 | 2 | 8 | 7 | 110 | 12 | 14 | 5 | 10 | 1 | 188 |
| **Sex (n)** | | | | | | | | | | | |
| **Male** | 9 | 2 | 4 | 3 | 75 | 5 | 9 | 2 | 4 | 1 | 115 (61,2) |
| **Female** | 10 | - | 4 | 4 | 35 | 7 | 4 | 3 | 6 | - | 73 (38,8) |
| **Consanguinity (n)** | 17 | 1 | 6 | 7 | 24 | 12 | 6 | 3 | 8 | 1 | 85 (45,2) |
| **Family history (n)** | 11 | - | 2 | 5 | 23 | 7 | 6 | 2 | 4 | - | 60 (31,9) |
| **Clinical symptomatic (n)** | 18 | 2 | 6 | 7 | 61 | 11 | 9 | 2 | 10 | 1 | 128 (68) |
| **Severe bleeding (n)** | | | | | | | | | | | |
| **CNS** | 7 | 1 | - | - | 10 | 4 | - | - | 4 | 1 | 27 (77,1) |
| **GIS** | 2 | - | 1 | 2 | 1 | 1 | - | - | - | - | 7 (20) |
| **Iliopsoas** | - | - | - | - | - | - | - | - | 1 | - | 1 (2,9) |
| **Total (%)** | 9 (47,4) | 1 (50) | 1 (12,5) | 2 (28,6) | 11 (10) | 5 (41,7) | - | - | 5 (50) | 1 (100) | 35 (18,6) |
| **Factor activity (n)** | | | | | | | | | | | |
| **<5%** | 8 | 1 | 5 | 1 | 24 | 9 | 6 | 4 | 4 | 0 | 62 (33) |
| **5%-30%** | 8 | 1 | 3 | 6 | 48 | 2 | 5 | 1 | 6 | 1 | 81 (43) |
| **30%-50%** | 3 | 0 | 0 | 0 | 38 | 1 | 3 | 0 | 0 | 0 | 45 (24) |
| **First bleeding age (n)** | | | | | | | | | | | 128 |
| **<1 month** | 11 | 0 | 0 | 1 | 6 | 1 | 1 | 0 | 7 | 0 | 27 (21) |
| **1 month-1 year** | 4 | 0 | 0 | 2 | 10 | 4 | 0 | 0 | 0 | 1 | 21 (16,4) |
| **1-5 years** | 3 | 1 | 3 | 3 | 14 | 6 | 7 | 1 | 1 | 0 | 40 (31,3) |
| **>5 years** | 0 | 1 | 3 | 1 | 31 | 0 | 1 | 1 | 2 | 0 | 40 (31,3) |
| **First diagnosis age (n)** | | | | | | | | | | | |
| **<1 month** | 11 | 0 | 0 | 1 | 7 | 0 | 1 | 0 | 4 | 0 | 24 (12,8) |
| **1 month-1 year** | 3 | 0 | 0 | 1 | 7 | 3 | 0 | 0 | 2 | 1 | 17 (9) |
| **1-5 years** | 4 | 1 | 4 | 2 | 29 | 8 | 8 | 0 | 1 | 0 | 58 (30,9) |
| **>5 years** | 1 | 1 | 4 | 3 | 67 | 1 | 4 | 5 | 3 | 0 | 89 (47,3) |

F; factor, CNS; central nervous system, GIS; gastrointestinal system.

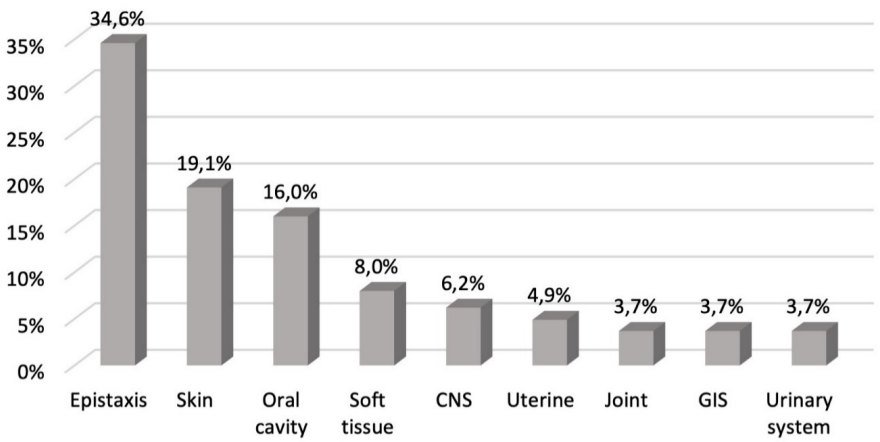


**Figure 1: The bleeding prevalence rates of the patients with rare coagulation factor deficiencies. CNS, central nervous system; GIS, gastrointestinal system.**

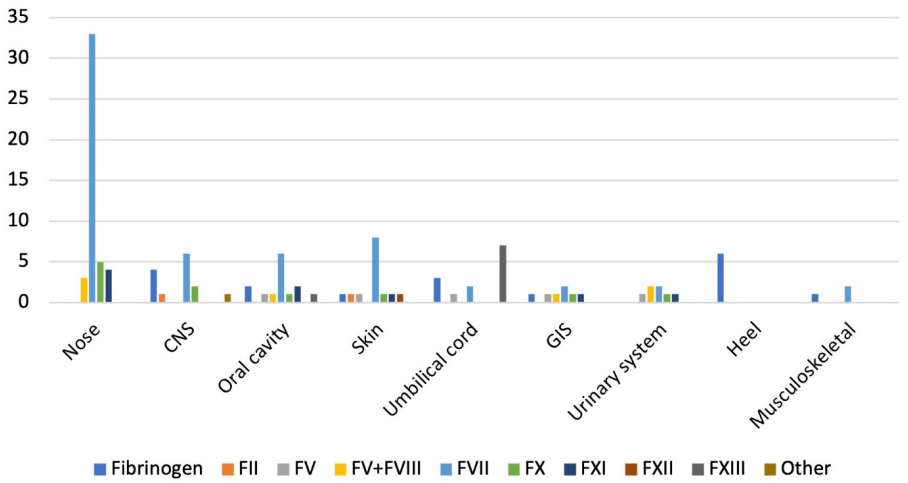


**Figure 2: The distribution of first bleeding sites in patients with rare coagulation factor deficiencies. F; factor, CNS; central nervous system, GIS; gastrointestinal system.**

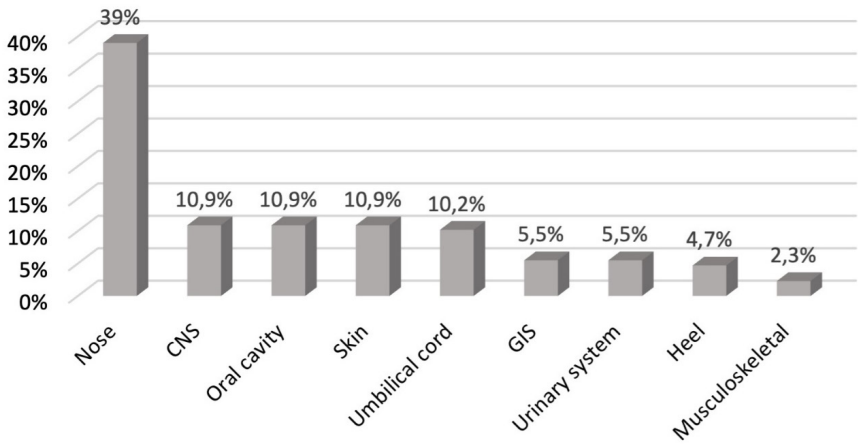


**Figure 3: First bleeding sites of patients with rare coagulation factor deficiencies. CNS; central nervous system, GIS; gastrointestinal system.**

**Table 2: Distribution of RFD patients according to the first bleeding sites**

| | Fibrinogen deficiency | FII deficiency | FV deficiency | FV+VIII deficiency | FVII deficiency | FX deficiency | FXI deficiency | FXII deficiency | FXIII deficiency | FVII+FIX deficiency | Overall n (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Nose (n)** | - | - | 1 | 3 | 33 | 5 | 4 | 1 | 2 | - | 50 (39) |
| **CNS (n)** | 4 | 1 | - | - | 6 | 2 | - | - | - | 1 | 14 (10,9) |
| **Oral cavity (n)** | 2 | - | 1 | 1 | 6 | 1 | 2 | - | 1 | - | 14 (10,9) |
| **Skin (n)** | 1 | 1 | 1 | - | 8 | 1 | 1 | 1 | - | - | 14 (10,9) |
| **Umbilical cord (n)** | 3 | - | 1 | - | 2 | - | - | - | 7 | - | 13 (10,2) |
| **GIS (n)** | 1 | - | 1 | 1 | 2 | 1 | 1 | - | - | - | 7 (5,5) |
| **Urinary system (n)** | - | - | 1 | 2 | 2 | 1 | 1 | - | - | - | 7 (5,5) |
| **Heel (n)** | 6 | - | - | - | - | - | - | - | - | - | 6 (4,7) |
| **Musculoskeletal (n)** | 1 | - | - | - | 2 | - | - | - | - | - | 3 (2,3) |

RFD; rare factor deficiency, F; factor, CNS; central nervous system, GIS; gastrointestinal system.

in the first month, 37.5% <1 year old, 68.8% <5 years old, and 52.7% of all patients (188) were diagnosed before 5 years old.

35/188 (18.6%) patients had at least one life-threatening bleeding, the most common were CNS (n:27, 77.1%), GIS (n:7, 20%) and iliopsoas (n:1, 2.9%) bleedings, respectively. CNS bleeding was found to be most common in patients with fibrinogen (n:7, 25.9%), FVII (n:10, 37%), FX (n:4, 14.8%), and FXIII (n:4, 14.8%) deficiencies (Table 1). Among the reasons leading to the diagnosis; bleeding (57.4%), preoperative screening (15.4%), incidental (15.4%), family history (6.4%), and postoperative bleeding (5.3%) (Figure 5). In addition, 2/5 (40%) patients with factor XII deficiency also had mucocutaneous bleeding symptoms.

as Turkey, it represents about 3-5% of all hereditary bleeding disorders (16). There was consanguinity between the parents in approximately half of our patients. Since the deficiencies of some factors can be asymptomatic, its exact frequency is not known. Its estimated prevalence in the world is about 1/1.000.000. Among these, FVII deficiency is the most common with a prevalence of 1/300,000-500,000, while FII deficiency is the rarest with a prevalence of 1/2,000,000 (3). FVII deficiency patients constituted half of our patients, and FII deficiency was rarer, observed in only two patients in the sample size reported herein.

Unlike the more common hemophilia (FVIII or FIX deficiency) and vWF deficiency, RFD has a broad clinical spectrum and

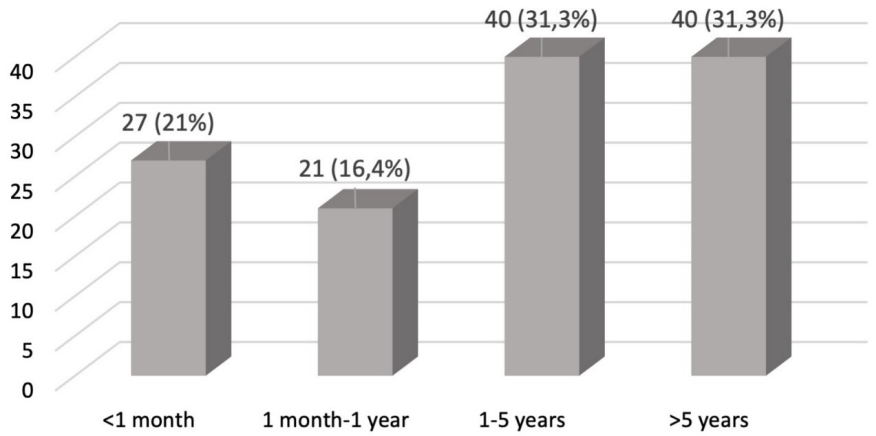


**Figure 4: The distribution of first bleeding age of the patients with rare coagulation factor deficiencies**

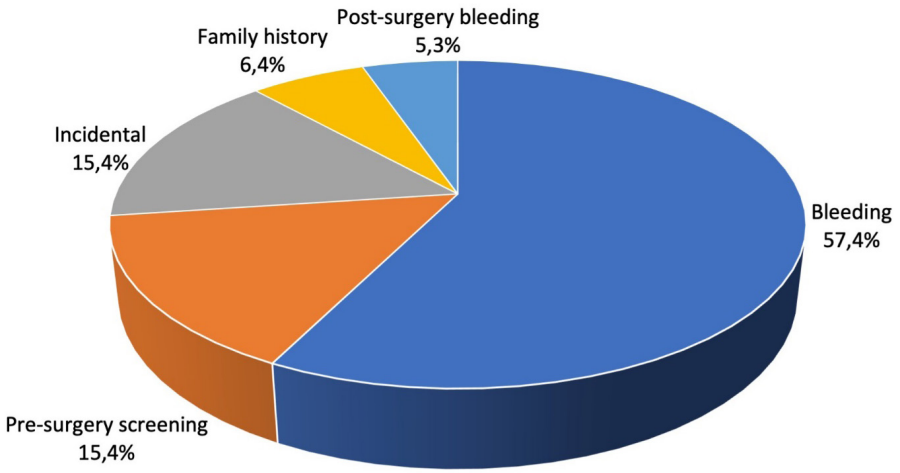


**Figure 5: Factors leading to diagnosis of the patients with rare coagulation factor deficiencies.**

## DISCUSSION

RFDs are a group of autosomal recessive bleeding disorders with the exception of dysfibrinogenemia. RFDs are characterized by the absence or dysfunction of one or more of the coagulation factors of the coagulation cascade. Although it is more common in societies where consanguineous marriages are common such

treatments are not clearly specified. Patients with mild bleeding symptoms may be diagnosed with delay or with life-threatening bleeding such as CNS bleeding (17). Almost half of the patients remained symptomatic at some point in their lives (18). In our study, 128 out of 188 patients were symptomatic, and 61% of them had symptoms in the last year. Bleeding is a predominant manifestation of the RFDs. Most of the patients

are asymptomatic, and the time of diagnosis is delayed. Tugcu et al. showed that 90% of asymptomatic cases were diagnosed with pre-surgical screening or family history (19). Also, 87.5% of our patients were diagnosed with pre-operative screening, incidentally or with family history.

RFDs are generally inherited autosomal recessively; therefore, homozygous individuals are symptomatic; on the other hand, mild to moderate bleeding symptoms can be seen in heterozygous individuals, but FVII deficiency is still incompatible with the factor level (4). Among our FVII deficiency cases, recurrent bleeding was observed in individuals with mildly low factor levels. Thrombotic events, impaired wound healing and early pregnancy loss may be accompanied, especially with fibrinogen and FXIII deficiencies (20). Moreover, the frequency of serious thromboembolic events has been reported to be 1 to 8% of patients with FXII deficiency. Demidova et al. observed mild mucocutaneous hemorrhages with FXII deficiency, which was also corroborated in our patient cohort, (2 out of 5 patients with FXII deficiency) (10). In newborns, bleeding after umbilical cord separation and heel blood collection is a common finding, and CNS bleeding may also be seen with high frequency. Common clinical findings in older children and adults are mucocutaneous (nose, oral cavity, and skin), menstrual, trauma or post-surgical bleeding, and muscle and joint bleeding (21). Uterine bleeding is seen in more than half of female RFD patients (16). Also, CNS and GIS bleedings are well-known common presentations of FX deficiency (8).

In the literature, the first bleeding sites for RFD patients have been reported to be the mucocutaneous, CNS, soft tissue, joints, urinary system, and GIS (12, 15, 19). Epistaxis was the most common (39%), and umbilical stump bleeding was identified most frequently in fibrinogen and FXIII deficiencies in this manuscript. Furthermore, heel bleeding was the most common initial bleeding symptom in hypofibrinogenemia cases. In most studies, the CNS is shown as the first bleeding site, most commonly in fibrinogen, FVII, FX, and FXIII deficiencies, and similar results except for FXIII were obtained in this study (8, 15, 19).

Contrary to common factor deficiencies, life-threatening hemorrhages such as CNS and GIS bleeding are not uncommon in RFDs. In our study, life-threatening bleeding occurred at least once in 18.6% of the patients, and the most common bleeding sites were the CNS (77.1%), GIS (20%) and iliopsoas (2.9%), respectively. Tugcu et al. showed that CNS bleeding was the most common with 41%, and joint, GIS, and iliopsoas bleeding in life-threatening events. (19). The CNS bleedings are expected in only about 3–5% of patients with hemophilia; however, this rate is over 10% in patients with RFDs (12, 15, 19, 22). Additionally, Siboni et al. showed that approximately 70% of bleeding occurs spontaneously and can be recurrent (6). CNS hemorrhage was observed in 27/188 (%14,4) patients in our study.

The age of initial complaint in RFDs varies depending on the factor level and the missing factor. In general, fibrinogen, FX, FXIII, and severe FVII deficiencies are symptomatic in the first years of life, while FV, FXI, XII, and mild FVII deficiencies become symptomatic at later ages (18, 21). In the current study, 1/3 of the patients began to have complaints under age 1, and most of them were fibrinogen, FVII, FX and FXIII deficiencies. Thirty-one (77.5%) of the 40 patients who became symptomatic at >5 years old had FVII deficiency. This is because the factor activity level of 78.2% of FVII deficiency was >5%. Moreover, frequent, severe, or chronic bleeding in RFDs can lead to anemia and iron deficiency. Even minor bleeding, such as nosebleeds, can cause iron deficiency if it occurs over longer periods of time. In a series of 294 patients, it was shown that anemia occurs in up to half of the bleeding episodes in homozygotes, mostly with factor II, V, or X deficiency (23).

Our study has some limitations. Our cohort could have been larger. The factor levels of the patients were variable, and severe deficiencies were rare. The majority of the patients had FVII deficiency. These patients were asymptomatic because of heterozygosity. Genotype-phenotype correlation could not be performed, because of lack of genetic analysis for most of the patients due to cost.

## CONCLUSION

In conclusion, the clinical symptoms of RFDs can vary significantly from one disease to another and from one patient with the same disorder to another. Although it is a rare disease group, it has high mortality and morbidity in affected individuals. Unfortunately, in severe deficiencies, it may be diagnosed with life-threatening bleeding in the newborn, or in asymptomatic cases, it may be life-threatening with heavy bleeding after surgery. For these reasons, awareness, early diagnosis, and prompt treatment are critical for RFDs.

**Ethics Committee Approval:** This study was approved by the Ethics Committee of Erciyes University (Approval number: 2023/350).

**Informed Consent:** Written consent was obtained from the patients and their relatives.

**Peer Review:** Externally peer-reviewed.

**Author Contributions:** Conception/Design of Study- V.G., E.Ü., E.P.Ş., H.T., C.A., K.K., D.A.T., T.P.; Data Acquisition- V..G, F.T.M., A.C.Ö., A.Ş., B.A., H.B.Ü., A.Ö.; Data Analysis/Interpretation- E.Y., S.A., M..K, A.F.Ö., Ü.Ç., E.Ü.; Drafting Manuscript- V.G., E.P.Ş, C.A., F.T.M., A.C.Ö., A.Ş., B.A., H.B.Ü. A.Ö., M.K.; Critical Revision of Manuscript- E.Ü., H.T., K.K., D.A.T., E.Y., A.F.Ö., Ü.Ç., E.Ü., T.P.; Final Approval and Accountability- V.G., E.P.Ş., H.T., F.T.M., C.A., K.K., D.A.T., A.C.Ö., A.Ş., B.A., H.B.Ü., A.Ö., E.Y., S.A., M.K., A..FÖ., Ü.Ç., E.Ü., T.P.

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